

Double Addition of Diphenylcyclopropenone to Azomethine Imines Generated from 6-Aryl-1,5-diazabicyclo[3.1.0]hexanes

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The formal [2+3] cycloaddition of a twofold excess of diphenylcyclopropenone to azomethine imines generated from 6-aryl-1,5-diazabicyclo[3.1.0]hexanes **1** under thermolysis conditions presumably occurs via the initially formed unstable dipolar bicyclic intermediates **4**. Isomerization of these

intermediates and subsequent addition of the second molecule of diphenylcyclopropenone with the extrusion of one molecule of carbon monoxide results in the formation of tricyclic 4a,7b-diazacyclopenta[cd]inden-7-ones **8** in good yields.

Introduction

During the last few years the thermal behavior of bicyclic diaziridines 6-R-1,5-diazabicyclo[3.1.0]hexanes has been the subject of systematic investigations in our group. We have established that a thermal diaziridine ring opening in these compounds leads to the intermediate formation of labile azomethine imines. These can be stabilized by a proton shift to form 1-arylmethyl- or 1-alkyl-2-pyrazolines,^[1] or by the formation of cycloaddition products, when the thermolysis is carried out in the presence of 1,3-dipolarophiles such as *N*-arylmaleimides^[2,3] or aryliso(thio)cyanates.^[4] A catalytic ring opening in the parent 1,5-diazabicyclo[3.1.0]hexane in the presence of boron trifluoride–diethyl ether, in contrast to the thermal reaction, leads to the formation of dimeric species instead of 1-methyl-2-pyrazoline.^[5]

As far as we are aware, reactions of diphenylcyclopropenone with *N,N'*-disubstituted diaziridines are not yet known. The reaction of diphenylcyclopropenone with, for example, aziridines depends on the substituents. If these substituents are not able to stabilize a 1,3-dipolar intermediate, no thermally induced electrocyclic opening occurs and the aziridine behaves as a base to attack a carbonyl atom of diphenylcyclopropenone. If the substituents can stabilize a 1,3-dipolar intermediate, however, 1,3-dipolar cycloaddition to the cyclopropenone double bond takes place with the formation of dihydropyridazines (at room temperature) or 2,5-dihydropyrroles as a result of CO extrusion (in boiling toluene).^[6] The reaction of diphenylcyclopropenone with 1,3-dipoles may also result in the formation of stable betaine-like structures.^[7] Finally, diphenylcyclo-

propenone can react with imines to afford addition products to a carbon-nitrogen double bond (see ref.^[8] and references therein).

In the present paper we report our results on the thermal reaction of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes with diphenylcyclopropenone as the 1,3-dipolarophile.

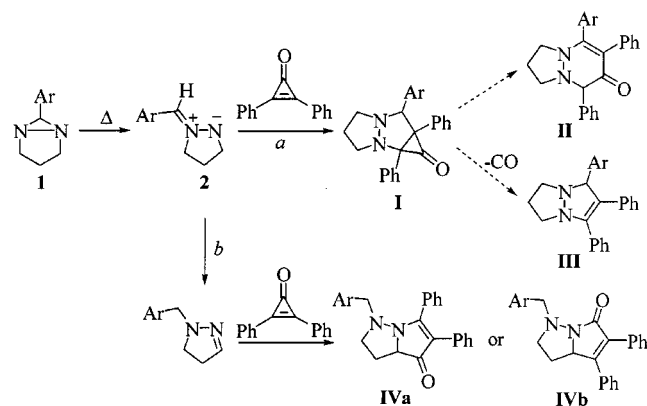
Results and Discussion

In accordance with the known thermal reactivity behavior of 6-aryl-1,5-diazabicyclo[3.1.0]hexanes and diphenylcyclopropenone (DPCP) we could expect at least two main reaction pathways for their reaction: The first way **a** (Scheme 1) is a direct reaction of DPCP with an initially formed azomethine imine **2**. This could proceed by an addition to the DPCP C–C double bond to give tricycle **I** and then an adduct **II** after a ring expansion and proton shift, or adduct **III** after CO extrusion. The second way **b** could be a reaction between DPCP and 2-pyrazoline as a product of azomethine imine isomerization, if DPCP reactivity as a 1,3-dipolarophile was insufficient. In this case adduct **IVa** or **IVb** with the reversed regiochemistry would be formed by analogy with the literature.^[8] A cycloaddition product with a stoichiometry of 1:1 was proposed.

An experiment with equimolar quantities of DPCP and 6-(4-methoxyphenyl)-1,5-diazabicyclo[3.1.0]hexane **1a** was carried out in boiling xylene for the 20 min needed for the decomposition of the starting diaziridine.^[3] After crystallization from benzene/hexane (1:1) we isolated a crystalline compound in ≈40% yield. Elemental analysis gave a molecular formula of C₄₀H₃₄N₂O₂, which is consistent with the general reaction C₁₁H₁₄N₂O (**1a**) + 2C₁₅H₁₀O (2 × DPCP) – CO = C₄₀H₃₄N₂O₂. To prove a “double addition” of DPCP we carried out this reaction with a twofold excess of DPCP and obtained the same product in a yield of 57%.

The ¹H NMR spectrum of the adduct contained signals of aromatic protons in the region δ = 6.8–7.6 (24 H) with

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Scheme 1. Possible cycloaddition reactions of ylide **2** with diphenylcyclopropanone

a doublet of doublets at $\delta = 6.85$ and 7.47 ($J = 7.5$ Hz) for the *p*-methoxy-substituted phenyl ring and another doublet of doublets at $\delta = 5.26$ (1 H, NCHCH_2), two doublets for the vicinal protons (1 H each) at $\delta = 4.55$ and 4.27 , a singlet for the methoxy group at $\delta = 3.80$, and a few multiplets for the other aliphatic protons in the region $\delta = 2.0$ – 3.0 (multiplicity of signals and different chemical shifts due to pseudo-axial and equatorial protons). In the ^1H NMR spectrum of the reaction mixture we did not observe any signals of 1-benzyl-2-pyrazoline or any other by-products in appreciable quantities. We were surprised to find only two methylene groups in the ^{13}C NMR spectrum of this adduct instead of the trimethylene bridge of the starting diazabicyclohexane. This indicates that an insertion of the reagent into the alkyl ring chain had taken place.

To avoid a spin-spin coupling preventing a clear structure determination, we synthesized a 3,3-dimethyl analogue of compound **1a** which allowed us to simplify the ^1H NMR spectrum and to give a definitive structural assignment. Moreover, the adduct of DPCP with compound **1b** formed good quality crystals after recrystallization from acetone/hexane/ether, so that an X-ray crystal-structure analysis could be performed;^[9] this proved the relative configuration of the adduct **8b** with a boat-shaped six-membered ring (Figure 1).

Other products of diphenylcyclopropanone cycloaddition to the 1,5-diazabicyclo[3.1.0]hexanes **1c–e** were prepared in the same manner as for compounds **1a,b**. Crystallization or column chromatographic workup of the reaction mixtures afforded the tricyclic compounds **8a–e** in yields of between 51 and 63%. The total reaction time depended only on the diazabicyclohexanes **1a–e** and generally took about 20–30 min [Equation (1)]. Almost the same results were obtained for the thermolysis at 110°C in toluene.

It is interesting to speculate about the mechanism of the reaction leading to **8**. We have established that the rate-determining step is the thermolysis of 6-aryl-1,5-diazabicyclohexanes to the labile *trans*-azomethine imine **2**.^[3] 1,3-Dipolar cycloaddition of diphenylcyclopropanone to the intermediate azomethine imine **2**, by analogy with the literature data,^[7] should result in the formation of adduct **3**. This un-

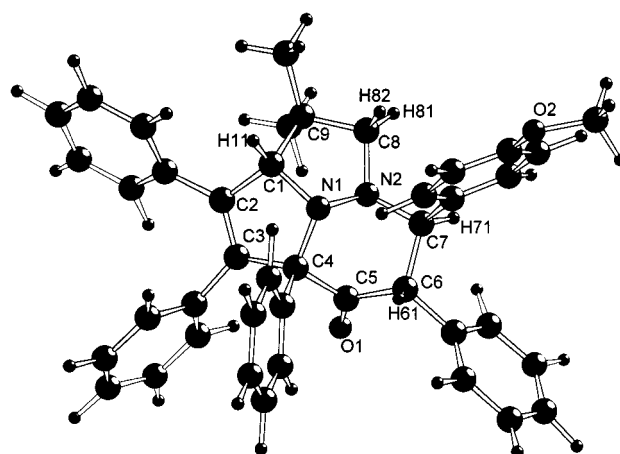
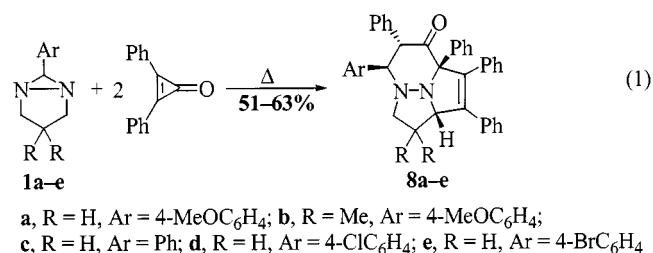


Figure 1. Structure of **8b** in the crystal; $\text{C}_{42}\text{H}_{38}\text{N}_2\text{O}_2$, monoclinic crystals of space group $P2_1$ (no. 4), $0.5 \times 0.3 \times 0.2$ mm, $Z = 2$, $D_c = 1.174(1)$ g/cm³, cell dimensions: $a = 998.0(3)$, $b = 1318.2(4)$, $c = 1331.8(5)$ pm, $\beta = 103.26(3)^\circ$, $V = 1.7054(20)$ nm³, 2965 reflections, room temp., $\mu = 0.08$ mm⁻¹, $F(000) = 640$, Mo- K_α , $\lambda = 71.07$ pm, graphite monochromator, $\theta_{\text{max}} = 30^\circ$

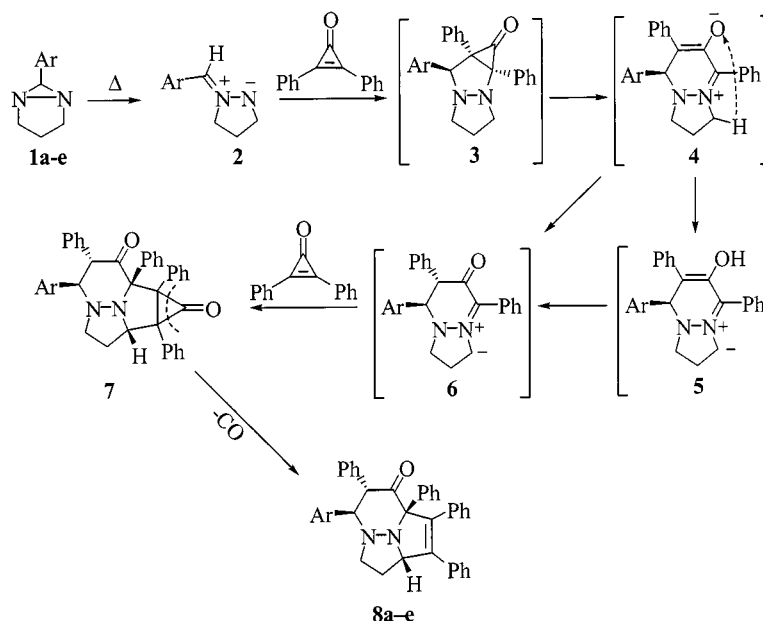


dergoes a ring expansion to give a nonstabilized zwitterionic species **4**. Intermediate **4** can rearrange by a 1,5-sigmatropic proton shift directly to the ylide **6** or via the enol **5** and subsequent tautomerization. The newly formed ylide **6** traps the second molecule of diphenylcyclopropanone to form the intermediate cyclopropanone **7**. Finally, this intermediate **7** expels carbon monoxide to form the resulting tricycle **8** with the shown stereochemistry (Scheme 2).

To determine if 2-pyrazolines are intermediates in the reaction described above, we treated 1-(4-methoxyphenyl)-2-pyrazoline formed in situ with DPCP under the standard reaction conditions. No product was obtained. Thus, it is evident that this reaction does not proceed via the intermediacy of 2-pyrazoline.

Conclusion

The results presented above show that a double addition of diphenylcyclopropanone to azomethine imines thermally generated from 6-aryl-1,5-diazabicyclo[3.1.0]hexanes offers a viable means of synthesizing 4a,7b-diazacyclopenta[*c-d*]inden-7-ones **8** in good overall yields. The structure of adduct **8b** was verified by X-ray crystallography. A well

Scheme 2. Stepwise reaction as a possible explanation for the formation of **8**

conceived “tandem” methodology should allow the synthesis of new, hitherto inaccessible tricyclic fused systems. In particular, we are continuing to study the reaction with unsymmetrically substituted cyclopropenones to clarify the regiochemistry of this unusual double cycloaddition.

Experimental Section

General Methods: NMR spectra were recorded on a Bruker DPX300 spectrometer at 300 MHz (^1H) or 75.5 MHz (^{13}C) in CDCl_3 . Chemical shifts δ are reported in ppm relative to residual CHCl_3 (^1H : $\delta = 7.26$) or CDCl_3 (^{13}C : $\delta = 77.0$) as internal standard. IR spectra were obtained on an UR-20 spectrometer. Melting points are uncorrected. All reagents and solvents were purified when necessary by standard procedures. 6-Aryl-1,5-diazabicyclo[3.1.0]hexanes (**1a,c–e**) were prepared by a condensation of the appropriate benzaldehyde with 1,3-diaminopropane and subsequent oxidation of the intermediate hexahydropyrimidine in accordance with the procedures described earlier.^[2,3] 1,5-Diazabicyclo[3.1.0]hexane (**1b**) was prepared as described below.

6-(4-Methoxyphenyl)-3,3-dimethyl-1,5-diazabicyclo[3.1.0]hexane (1b): 4-Methoxybenzaldehyde (4.5 mL, 37 mmol) was dissolved in a mixture of EtOH (15 mL) and H_2O (7.5 mL) and the mixture added slowly (1 h) to stirred and water-ice cooled 2,2-dimethyl-1,3-propanediamine (4.2 g, 41 mmol). After the addition was complete, the mixture was stirred for 1.5 h at room temperature. After that, the EtOH was removed under reduced pressure. The residue was cooled in an ice-water bath and 21.3 mL of 2.35 N NaOCl (0.05 mol) was added over 15 min with vigorous stirring. After the addition was complete, the mixture was vigorously stirred for 45 min at room temperature. Then, the mixture was extracted with benzene, washed three times with water, and the benzene solution was dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo. Crystallization of the residue from ether with the addition of a small amount of hexane gave 4.6 g (57%) of **1b**, m.p. 59–60 °C, $R_f = 0.36$ (Et_2O). IR (CHCl_3): $\tilde{\nu} = 3030\text{ cm}^{-1}$, 2970, 2940, 2880,

2840, 1625, 1590, 1520, 1470, 1440, 1390, 1370, 1310, 1260, 1175, 1140, 1110, 1040, 1005, 960, 880. ^1H NMR (300 MHz, CDCl_3), $\delta = 1.23$ (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 2.96 (d, $J = 11.0$ Hz, 2 H, NCH_2), 3.25 (d, $J = 10.6$ Hz, 2 H, NCH_2), 3.38 (s, 1 H, CH), 3.80 (s, 3 H, OMe), 6.87 (d, $J = 8.8$ Hz, 2 H, Ar), 7.24 (d, $J = 8.8$ Hz, 2 H, Ar).

General Experimental Procedure for the Synthesis of Compounds 8a–8e: A mixture of 6-aryl-1,5-diazabicyclo[3.1.0]hexane (**1a–e**) (1 mmol) and 2,3-diphenylcyclopropenone (2 mmol, twofold excess) in dry *p*-xylene was stirred and heated at 140 °C (bath temperature). The solvent was evaporated in vacuo, and the residue was crystallized from the appropriate solvent or purified by column chromatography on silica gel to give (**8a–e**).

rel-(2aR,5S,6R,7aR)-5-(4-Methoxyphenyl)-1,2,6,7a-tetraphenyl-3,4,5,6,7,7a-hexahydro-2aH-4a,7b-diazacyclopenta[cd]inden-7-one (8a): 6-(4-Methoxyphenyl)-1,5-diazabicyclo[3.1.0]hexane (**1a**) was heated for 20 min in 6 mL of xylene. Crystallization from benzene/hexane (1:1). Yield 0.325 g (57%) of **8a**, m.p. 241–242 °C (dec), $R_f = 0.74$ (THF/hexane, 1:1). IR (CHCl_3): $\tilde{\nu} = 3070\text{ cm}^{-1}$, 3040, 3010, 2960, 2940, 2920, 2890, 2860, 2840, 1750 (C=O), 1620, 1580, 1515, 1500, 1455, 1445, 1305, 1290, 1260, 1180, 1120, 1090, 1040. ^1H NMR (300 MHz, CDCl_3), $\delta = 2.15$ (m, 1 H, NCH_2CH_2), 2.37 (m, 2 H, NCH_2 , NCH_2CH_2), 2.95 (m, 1 H, NCH_2), 3.80 (s, 3 H, OCH₃), 4.27 (d, $J = 7.9$ Hz, 1 H, CH), 4.55 (d, $J = 7.9$ Hz, 1 H, CH), 5.26 (m, 1 H, NCH), 6.85 (d, $J = 7.5$ Hz, 2 H, Ar), 7.0–7.35 (20 H), 7.47 (d, $J = 7.5$ Hz, 2 H, Ar). ^{13}C NMR (75.5 MHz, CDCl_3 , DEPT): $\delta = 31.6$ (–, CH_2), 48.5 (–, CH_2), 55.6 (+, OCH₃), 59.9 (+, CH), 71.2 (+, CH), 71.6 (+, CH), 93.7 (C_{quat}), 113.8, 127.2, 127.5, 127.9, 128.3, 128.6, 128.7, 128.8, 129.9, 130.0, 131.3, 132.5, 134.8, 136.1, 136.2, 139.3, 139.4, 140.5, 159.7, 206.1 (C=O). $\text{C}_{40}\text{H}_{34}\text{N}_2\text{O}_2$ (574.7): calcd. C 83.59, H 5.96, N 4.87; found C 83.63, H 6.09, N 4.93.

rel-(2aR,5R,6S,7aS)-5-(4-Methoxyphenyl)-3,3-dimethyl-1,2,6,7a-tetraphenyl-3,4,5,6,7,7a-hexahydro-2aH-4a,7b-diazacyclopenta[cd]inden-7-one (8b): 6-(4-Methoxyphenyl)-3,3-dimethyl-1,5-diazabicyclo[3.1.0]hexane (**1b**) was heated for 20 min in 6 mL of

xylene. Crystallization from acetone/ether (1:1) containing a small amount of hexane gave 0.21 g of **8b**. The mother liquor was purified by column chromatography on silica gel (hexane/ethyl acetate, 3:1) to give an additional 0.097 g of **8b**. Overall yield 0.307 g (51%), m.p. 270–273 °C, R_f = 0.75 (ethyl acetate/hexane, 1:2). ^1H NMR (300 MHz, CDCl_3), δ = 1.02 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 2.26 (d, J = 9.0 Hz, 1 H, N- CH_2), 2.49 (d, J = 9.0 Hz, 1 H, N- CH_2), 3.80 (s, 3 H, OCH_3), 4.19 (d, J = 7.5 Hz, 1 H, CH), 4.49 (d, J = 7.5 Hz, 1 H, CH), 5.06 (s, 1 H, NCH), 6.83 (d, J = 8.6 Hz, 2 H, Ar), 6.88–7.32 (20 H), 7.39 (d, J = 8.6 Hz, 2 H, Ar). ^{13}C NMR (75.5 MHz, CDCl_3 , DEPT): δ = 25.9 (+, CH_3), 28.7 (+, CH_3), 42.3 [$\text{C}(\text{CH}_3)_2$], 55.6 (+, OCH_3), 59.9 (+, CH), 63.8 (–, CH_2), 71.5 (+, CH), 82.2 (+, CH), 93.0 (C_{quat}), 113.7, 127.0, 127.1, 127.2, 127.3, 127.5, 127.8, 128.1, 128.5, 128.6, 128.7, 129.9, 130.1, 131.2, 132.6, 136.0, 136.6, 136.7, 138.8, 140.5, 142.1, 159.6, 205.8 (C=O). $\text{C}_{42}\text{H}_{38}\text{N}_2\text{O}_2$ (602.8): calcd. C 83.69, H 6.35, N 4.65; found C 83.65, H 6.40, N 4.59.

rel-(2aR,5S,6R,7aR)-1,2,5,6,7a-Pentaphenyl-3,4,5,6,7,7a-hexahydro-2aH-4a,7b-diazacyclopenta[cd]inden-7-one (8c): 6-Phenyl-1,5-diazabicyclo[3.1.0]hexane (**1c**) was heated for 25 min in 5 mL of xylene. Crystallization from acetone gave 0.22 g of **8c**. An additional 0.082 g of product was isolated by column chromatography on silica gel (eluent hexane/ethyl acetate, 2.5:1). Overall yield 0.302 g (55%), m.p. 268–270 °C (dec), R_f = 0.89 (Et_2O). IR (CHCl_3): $\tilde{\nu}$ = 3090 cm^{-1} , 3070, 3040, 3010, 2960, 2930, 2890, 2860, 1750 (C=O), 1610, 1500, 1455, 1285, 1090, 1040. ^1H NMR (300 MHz, CDCl_3), δ = 2.15 (m, 1 H, NCH_2CH_2), 2.40 (m, 2 H, NCH_2 , NCH_2CH_2), 2.95 (m, 1 H, NCH_2), 4.34 (d, J = 7.9 Hz, 1 H, CH), 4.62 (d, J = 7.9 Hz, 1 H, CH), 5.28 (m, 1 H, NCH), 7.0–7.63 (25 H). ^{13}C NMR (75.5 MHz, CDCl_3 , DEPT): δ = 31.4 (–, CH_2), 48.6 (–, CH_2), 59.7 (+, CH), 71.2 (+, CH), 72.1 (+, CH), 93.8 (C_{quat}), 127.2, 127.5, 128.0, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 129.9, 130.2, 132.5, 134.7, 136.1, 138.0, 139.3, 139.4, 140.4, 206.1 (C=O). $\text{C}_{39}\text{H}_{32}\text{N}_2\text{O}$ (544.7): calcd. C 86.00, H 5.92, N 5.14; found C 86.10, H 5.95, N 5.20.

rel-(2aR,5S,6R,7aR)-5-(4-Chlorophenyl)-1,2,6,7a-tetraphenyl-3,4,5,6,7,7a-hexahydro-2aH-4a,7b-diazacyclopenta[cd]inden-7-one (8d): 6-(4-Chlorophenyl)-1,5-diazabicyclo[3.1.0]hexane (**1d**) was heated for 30 min in 4 mL of xylene. The residue was purified by column chromatography on silica gel (eluent hexane/ethyl acetate, 4:1–1:1) to give 0.364 g (63%) of **8d**, m.p. 245–247 °C (dec.), R_f = 0.78 (ethyl acetate/hexane, 1:2). IR (CHCl_3): $\tilde{\nu}$ = 3085 cm^{-1} , 3070, 3010, 2965, 2930, 2890, 2860, 1750 (C=O), 1610, 1520, 1495, 1450, 1285, 1095, 1040, 1020. ^1H NMR (300 MHz, CDCl_3), δ = 2.15 (m, 1 H, NCH_2CH_2), 2.39 (m, 2 H, NCH_2 , NCH_2CH_2), 2.96 (m, 1 H, NCH_2), 4.22 (d, J = 8.0 Hz, 1 H, CH), 4.58 (d, J = 8.0 Hz, 1 H, CH), 5.29 (m, 1 H, NCH), 6.95–7.35 (22 H), 7.51 (d, J = 7.7 Hz,

2 H, Ar). $\text{C}_{39}\text{H}_{31}\text{ClN}_2\text{O}$ (579.1): calcd. C 80.88, H 5.40, N 4.84; found C 80.60, H 5.49, N 4.69.

rel-(2aR,5S,6R,7aR)-5-(4-Bromophenyl)-1,2,6,7a-tetraphenyl-3,4,5,6,7,7a-hexahydro-2aH-4a,7b-diazacyclopenta[cd]inden-7-one (8e): 6-(4-Bromophenyl)-1,5-diazabicyclo[3.1.0]hexane (**1e**) was heated for 30 min in 4 mL of xylene. Crystallization from acetone/ether (1:1) containing a small amount of hexane gave 0.272 g of **8e**. An additional 0.11 g of the product was isolated by column chromatography on silica gel (eluent hexane/ethyl acetate, 2:1). Overall yield 0.382 g (61%), m.p. 238–239 °C, R_f = 0.80 (ethyl acetate/hexane, 1:2). IR (CHCl_3): $\tilde{\nu}$ = 3070 cm^{-1} , 3035, 2970, 2930, 2890, 2860, 1750 (C=O), 1610, 1520, 1490, 1450, 1280, 1110, 1080, 1040, 1015. ^1H NMR (300 MHz, CDCl_3), δ = 2.15 (m, 1 H, NCH_2CH_2), 2.35 (m, 2 H, NCH_2 , NCH_2CH_2), 2.96 (m, 1 H, NCH_2), 4.20 (d, J = 7.7 Hz, 1 H, CH), 4.55 (d, J = 7.7 Hz, 1 H, CH), 5.28 (m, 1 H, NCH), 6.95–7.5 (24 H). $\text{C}_{39}\text{H}_{31}\text{BrN}_2\text{O}$ (623.6): calcd. C 75.12, H 5.01, N 4.49; found C 74.50, H 5.01, N 4.30.

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- [9] Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-167492. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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